

PREVENTIVE CARDIOLOGY

PREVENTION OF CONGENITAL HEART DISEASE

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CONGENITAL HEART DISEASE AS A PROBLEM:

Estimates of the incidence of congenital heart disease (CHD) vary from 2.3 to 7.0 per 1,000 live births, but it is well-known that the true incidence can only be estimated with some degree of accuracy when the live births are followed up longitudinally. Yerushalmy (1970) in the California Child Health & Development Study found that only 5 per 1,000 had demonstrable CHD at birth but close follow-up to age 5 years, revealed that the incidence had climbed to 9.3 per 1,000. It is, therefore, agreed by most workers that out of 100 live births, there would be 1 baby with CHD, and this makes it one of the commonest, if not the commonest significant congenital malformation found in live-borns, the usual accepted figure for the incidence of significant congenital malformations being 3 per 100 live-births.

CHD is not only a common malformation but exacts considerable morbidity and mortality. In the Department of Paediatrics of the University of Singapore, where there is an average annual admission rate of children 10 years age and under of 6,300, the over-all mortality rate is about 2-3%. The second commonest cause of death is CHD:- (Table I)

TABLE I

Year	Total admissions	Total deaths	Deaths due to		
			Pneumonia	CHD	Diarrhoea
1964	6,249	280	73	65	23
1965	6,528	233	81	67	25
1966	6,873	273	92	61	21
1967	6,586	244	62	53	25
1968	6,308	216	45	43	12
1969	6,524	179	42	32	16
1970	6,356	169	44	25	16
1971	6,380	158	31	33	10

Therefore, in terms of loss of life in Singapore, where family planning is extremely effective, CHD is a serious problem in spite of the availability of common surgical facilities. In terms of morbidity, it causes a considerable strain on the paediatric services, and in terms of suffering, both for the infants and their parents, CHD merits serious consideration from the point of view of prevention. The infants with CHD are just embarking on the road to life and many will be unable to contribute towards the Republic's welfare.

AETIOLOGY OF CHD:

Before primary prevention can be considered, the causes of CHD should be elicited. Unfortunately, the problem is not straightforward, but recent work has done much to give a better idea of probable causes.

A. ACQUIRED CAUSES:

1. Drugs taken by the pregnant mother
2. Irradiation of foetus

3. Intra-uterine infections
4. Dietary deficiency in pregnancy
5. Foetal hypoxia

B. GENETIC CAUSES:

1. Due to genes of large mutant effect
 - (a) Autosomal dominant
 - (b) Autosomal recessive
 - (c) Sex-linked
2. Due to chromosomal aberrations
3. Due to multi-factorial inheritance.

The acquired causes have been recently reviewed by Cruz *et al* (1971). No matter what the extrinsic factors may be, there is a critical period in foetal development when it is highly susceptible to teratogens, and it is during this period CHD may occur. This is the period when gastrulation and tubulation of the foetus take place. Prior to this, the blastulation period immediately after fertilisation is relatively resistant to teratogenic influences because damaged cells are replaced by other cells. Of course, if the extrinsic agents are severe, this results in death of the early foetus. This early blastula stage ends about the 11th to the 12th day after fertilisation, and gives way to gastrulation when organogenesis starts. This period of organogenesis renders the foetus most liable to teratogenesis. This is followed by another period of increased growth of the organs so formed, and again the foetus now becomes fairly resistant to the development of malformations. At the moment, it is still not clear why certain teratogens may produce CHD in one pregnant woman and not in another even with comparable doses and time of exposure. It is probable that there are many other factors which interact with the teratogens themselves producing the final result. Certainly, characteristics of the foetus itself have a great part to play in this determination, that is, there always is an interplay of the genes and environment in so-called extrinsic factors in the causation of CHD.

There is no doubt that drugs are capable of producing CHD as evidenced so clearly by the thalidomide tragedy. Equally, irradiation is also an undoubted cause given the correct time and dosage. The effect of dietary deficiency in the production of CHD is more convincingly proved in experimental animal situations rather than in humans, while the effect of generalised hypoxia, e.g. pregnant women living in high altitudes, is less certain. However, it is with regard to intra-uterine infections, as exemplified by rubella contracted by the pregnant mother during the first trimester that is most convincing. In the rubella outbreak in Singapore in 1969/1970, a total of 33 severely affected congenital rubella newborns were studied in the Department of Paediatrics, and 64% of them had evidence of CHD. The commonest lesion was a PDA, and all had evidence of cardiac failure in the neonatal period except one. 6 of the 33 cases died, and at autopsy, 5 of them had CHD, all with a PDA. One specimen showed evidence of a bifid apex (Tan *et al*, 1970) besides the PDA. In this outbreak, all the mothers except one, were unaware that they contracted German measles during pregnancy. Besides PDA; pulmonary artery stenosis, pulmonary valve stenosis, aortic valve stenosis, aberrant right subclavian artery and VSD have also been documented in infants with congenital rubella (Cooper *et al*, 1969). In their cardiac catheterisation and angiographic findings of 78 patients, they found the follow-

ing frequency of the various cardiac lesions in those with CHD:-

Patent ductus arteriosus	: 78%
Right pulmonary artery stenosis	: 70%
Left pulmonary artery stenosis	: 56%
Pulmonary valve stenosis	: 40%
Mild aortic valve stenosis	: 14%
Aberrant right subclavian artery	: 11%
Ventricular septal defect	: 10%

Many of the patients with congenital rubella who succumb in infancy, do so because of their cardiac lesions. Besides rubella, other viral infections during pregnancy may also cause CHD in the foetus, e.g. herpes simplex, cytomegalovirus, infective hepatitis, chickenpox, Coxsackie virus, etc.

With regard to the inheritance of CHD, much has been learnt recently. CHD transmitted through genes of large mutant effect, e.g. the mode of inheritance being autosomal dominant or recessive, or through sex-linkage, are usually part of a large disease entity. Marfan's disease consists of arachnodactyly and other skeletal deformities, dislocation of the lens and aortic and pulmonary incompetence with aneurysm, and is inherited in an autosomal dominant manner. The mucopolysaccharidoses may show evidence of cardiac disease especially mitral incompetence; the Hunter type being inherited in a sex-linked manner, while the Hurler, Schiee and Morquio varieties are autosomal recessive. Tuberosus sclerosis, an autosomal dominant disease, manifests with fits, mental deficiency and adenoma sebaceum, but the tuberosus nodules may also be found in the heart. Glycogen storage disease of the Pompe type affects mainly the heart and skeletal muscles and all the patients die in infancy of intractable cardiac failure or aspiration bronchopneumonia, the mode of inheritance being autosomal recessive. Subaortic stenosis can be genetic, and is then transmitted as an autosomal dominant. Muscular dystrophy (sex-linked) and, Freiderich's ataxia (autosomal recessive) may also affect the heart. Refsum's disease with polyneuritis and retinitis pigmentosa may also show arrhythmias—it is transmitted in an autosomal recessive manner. Holt-Oram syndrome with abnormalities of the limbs and ASD or VSD is inherited in an autosomal dominant manner. There are other diseases transmitted by genes of large mutant effect which also affect the heart. As mentioned before, the cardiac disease is usually only part of a more serious disorder.

Genetic diseases due to chromosome abnormalities may also affect the heart. In this regard, infants suffering from Down's anomaly with mental deficiency are often born with CHD, the commoner lesions being end-

ocardial cushion defects, VSD and PDA. In a series of 70 cases of this disease, the frequency of the various types of CHD was as follows (Rowe & Uchida, 1961):-

Endocardial cushion defects	: 36%
Ventricular septal defect	: 33%
Patent ductus arteriosus	: 10%
Secundum atrial septal defect	: 9%

Turner's Syndrome in the female is associated with coarctation of the aorta in approximately 20% of cases (Fergusson-Smith, 1965), but in this regard the association of Turner's Syndrome with the female phenotype and CHD is uncommon in Singapore (Wong, 1969) probably because coarctation itself is relatively uncommon here. However, Male Turner's Syndrome or Noonan's Syndrome is often associated with CHD. In a series of 8 cases studied by Wong (1968) there were 3 with CHD, i.e. about 40%. The commonest lesion was pulmonary stenosis. E-trisomy and D-trisomy syndromes also show a high frequency of associated cardiac malformations. In a series of 22 cases of E-trisomy, there were 17 patients with CHD, the commonest lesions being VSD, PDA, ASD and coarctation of the aorta (Wong, 1967).

In spite of the inheritance of CHD through genes of large mutant effect and its appearance in chromosomal abnormalities, the majority of CHD are not inherited through these mechanisms. In fact, doubt has been expressed whether any of them had a genetic basis at all, since a familial incidence of CHD is the exception rather than the rule. Yet, various studies have shown that CHD has a genetic basis. Nora *et al* (1967) found that 25% of monozygous twins were concordant for CHD when one member had the lesion, while in dizygous twins, it was concordant in only 4.9%. Similarly, Nora & Meyer (1966) in a survey of families with CHD found that 34% of 417 randomly selected patients also had one or more relatives with CHD, while the matched controls showed only 9% of families with CHD ($P < 0.01$). Furthermore, among siblings of those with CHD, 3.4% also were found to have CHD compared with none in the control group ($P < 0.001$). Therefore, the common isolated CHD's have a genetic basis. Yet, further study of such families reveal that it is not inherited in an autosomal dominant or recessive manner, nor is it sex-linked. Nora (1968) showed that the inheritance conformed with that associated with a multi-factorial mode of transmission; in other words, it is not one or two genes which determine its presence or absence but a whole group of genes interacting with each other as well as with environmental factors. This mode of inheritance can be explained by Fig. 1, which shows 2 curves of liability to CHD in 2 families. The vertical line represents the threshold beyond which CHD occurs in the foetus. The curve A, representing family A does not possess this liability, as it is well "leftward" of the threshold vertical line. On the other hand, family B as represented by curve B, has a certain portion beyond the threshold line, and the shaded portion is a measure of the liability to "contract" CHD. In such family, the constellation of interacting genes puts it at risk, yet many members will be free, except for the few who 'lie' to the right of the threshold line, determined in part also by environmental intra-uterine factors. This multi-factorial genetic hypothesis can be tested by extensive family studies, and, data being accumulated show that they are consistent with such a mode of inheritance. This type of inheritance accounts also for the aetiology of many other common congenital malformations such as hypertrophic pyloric stenosis, cleft lip and palate, Hirschsprung's disease, congenital dislocation of the hip, spina bifida cystica, etc. (Carter, 1969), which at one time, were thought to be wholly due to environmental factors. One of the main differences in genetic counselling for diseases due to genes of large mutant effect and those due to multi-factorial inheritance is that in the former, the risk is always identical in a family no matter how many affected offspring had

MULTIFACTORIAL INHERITANCE

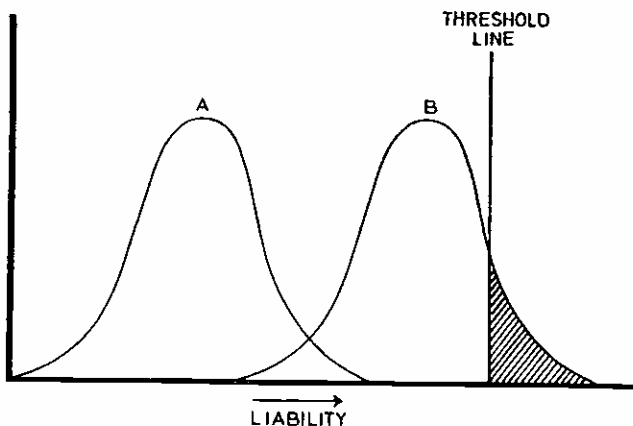


Fig. 1. Family A has no liability, while Family B shows this liability to a degree represented by curve beyond the threshold line. For explanation, see text.

been produced. For example, the risk for an autosomal recessive condition such as glycogen storage disease of the heart is 1 in 4 for an offspring to be so affected in a family proved to be at risk. If the unfortunate mother had given birth to 3 affected babies in the first 3 consecutive pregnancies, the risk for the 4th pregnancy being affected is still 1 in 4. The mother had just been unlucky in that the probability risk had worked against her on a chance basis, 3 times out of 3. This is not so with multi-factorial inheritance. If a mother had given birth to a child with CHD, a risk figure can be given on the following bases:-

1. The frequency of the CHD in a particular population. An approximate of the risk for the next offspring to be affected is given by the square root of this frequency (Edwards, 1960).
2. The number of affected offspring changes the risk because there is no way of knowing whether the family belongs to a curve "leftward" or "rightward" of the threshold line till another affected offspring appears. Then, it can be surmised that it is a "rightward" family when a 3rd affected offspring appears, the risk is still further increased.

PRIMARY PREVENTION OF CHD:

(a) ACQUIRED CAUSES:

Here, there are several ways whereby the medical profession may assist in prevention. Drugs should not be given to pregnant mothers especially in the first trimester of pregnancy, unless they really are necessary, and even then the types of drugs should be carefully scrutinised. They should not be given for longer than necessary. In Singapore, and areas around, cultural habits include self-medication for real or non-existent illnesses in pregnancy with indigenous herbs and powders which may contribute to the incidence of congenital malformations. Education of the public to abstain from such concoctions may help in this regard.

With regard to infections during pregnancy and CHD, the majority are virus diseases, and greater emphasis on research in the prevention of these diseases is needed. Both with regard to urgency and practicability, the prevention of congenital rubella should receive high priority. Vaccination of the female population against rubella has been carried out in some countries. In Singapore, we have embarked on a clinical trial of such a vaccine, and its efficiency is proved. In Singapore, 42% of women in the age group 15-30 years (Lee, 1972) are non-immune. This pool of non-immune women is much higher than that encountered in the West where the figure is around 20-25%. Pregnant women suspected of contracting rubella or those who have come into contact with rubella patients, could have their H-I rubella antibodies estimated, and if the results point to a fresh infection in a non-immune pregnant mother, therapeutic abortion can be carried out if such exposure occurred during the first trimester.

X-ray examination of the pregnant woman should be reduced to the minimum especially during the first trimester of pregnancy.

(b) GENETIC CAUSES:

In those genetic diseases with CHD due to genes of large mutant effect, genetic counselling should be offered. The probability risks of future affected offspring are explained to the parents. In this regard, if the risks are less than 1 in 30, they are small and probably well worth taking if the parents want a child badly. If the risks are more than 1 in 10, they are substantial and such a view can be communicated to the parents although the decision to proceed with further pregnancies or not rests with them. Risks which lie between can either be taken or not, depending on the attitudes of the parents themselves. However, genetic counselling to be effective must be undertaken actively,

and in our Department, genetic advice is offered not only to parents of affected offspring but also to the siblings of parents carrying affected genes, and if the mutant genes may produce severe diseases, advice is offered to prospective spouses of these siblings. Parents with affected offspring, and who are already pregnant when seeking genetic advice, are offered genetic studies on amniotic fluid obtained by amniocentesis if relevant e.g. sexing of foetus in sex-linked diseases, etc. The following diagram (Fig. 2) illustrates our scheme for genetic counselling.

Genetic diseases due to chromosomal abnormalities associated with CHD and where genetic advise may be useful, include Down's anomaly and E-trisomy, because in these 2 situations, familial cases can occur. Risk figures for recurrence can be given and amniocentesis studies are also relevant if the parents are already pregnant.

However, it is in the group of CHD's inherited in a multi-factorial manner that forms the bulk of cases. Risk figures are harder to obtain by the very nature of the mode of inheritance. However, a first approximation of risks in an empirical manner can be made if the frequency of the various types of CHD in a particular region is known. The first approximation of risks applies to the risk of another offspring being affected after the first affected is born. The following table (Table II) shows the frequency of cases of CHD encountered in the Department from 1964-1968 in the first column (Loh, 1969); the approximate risk based on the square root of the frequency (Edwards, 1960) in the second; and the comparable figures for the United States compiled by Nora (1972) in the third column:-

TABLE II

Type of CHD	% Frequency	Empiric risk figures %	
		Singapore	U.S.A.
Ventricular septal defect	31.4	5.6	5.0
Patent ductus arteriosus	13.0	3.6	3.5
Tetralogy of Fallot	9.4	3.0	3.2
Atrial septal defect	8.4	2.8	3.2
Transposition of great vessels	7.6	2.6	2.2
Pulmonary stenosis	7.0	2.4	2.9
Pulmonary atresia	3.1	1.7	1.0
Endocardial cushion defects	2.4	1.5	2.0
Coarctation of aorta	1.4	1.2	2.4
Aortic stenosis	1.2	1.1	2.1
Endocardial fibroelastosis	1.2	1.1	---
Tricuspid atresia	0.9	1.0	1.4
Ebstein's anomaly	0.7	0.8	0.7

It is admitted that broad assumptions have been made in the above approximations, viz. that the incidence of CHD in Singapore is taken as 1% of live births, and that the frequency of the various types of CHD seen in the Department is representative of the real frequency. Even then, it is rather surprising that the approximations are pretty close to those in the U.S., e.g. the risk of a family with one offspring with VSD having another child with VSD is 5.6% in Singapore and 5.0% in U.S., i.e. there is a 1 in 20 chance, and so on for the other abnormalities. This is a measure

GENETIC CLINIC SET-UP:

The general chronology of investigation of involved families is shown below:-

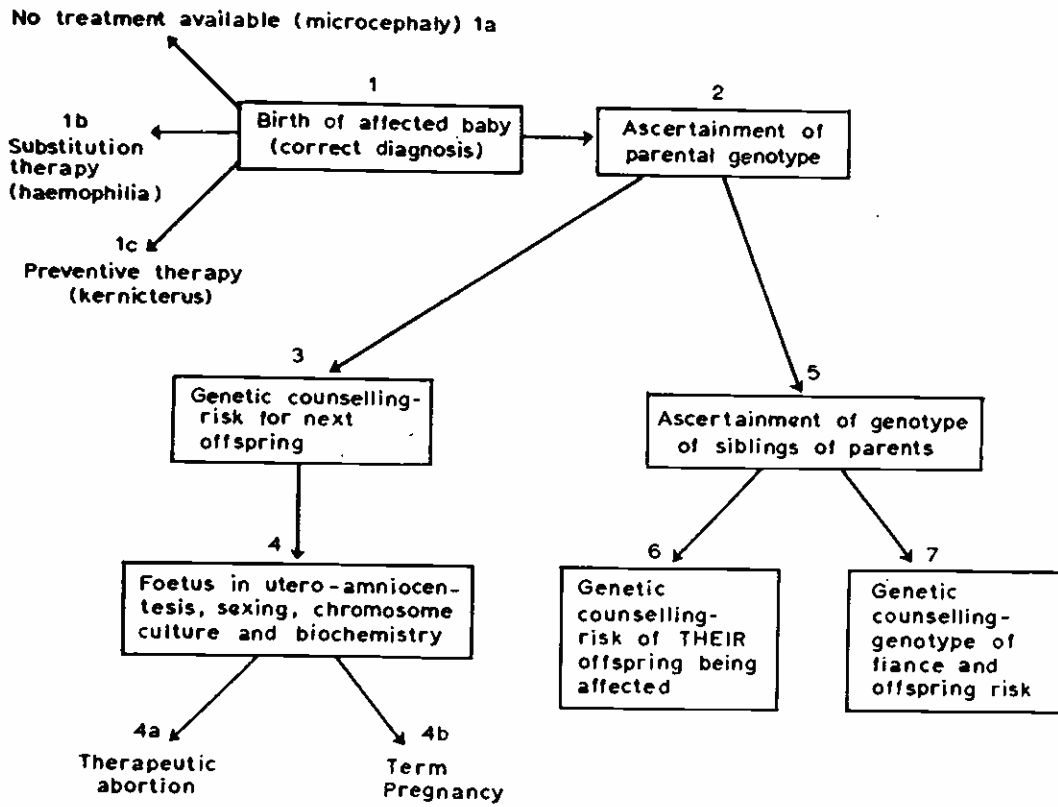


Fig. 2. Scheme for counselling applied to genetic diseases in Division of Medical Genetics, Dept. of Paediatrics, University of Singapore.

FAMILY P: CHD

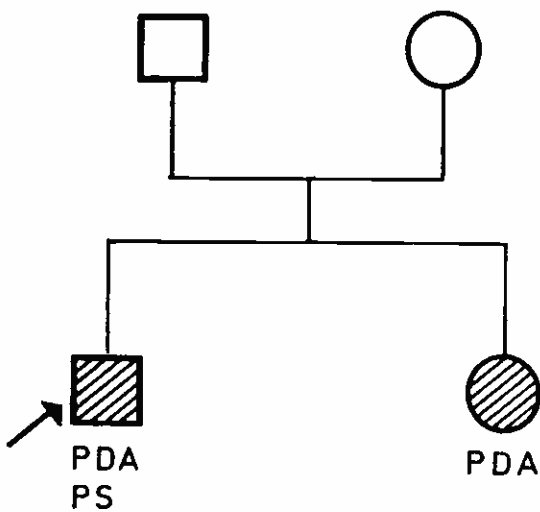


Fig. 3. Family with both offspring with C.H.D.

FAMILY Q: CHD

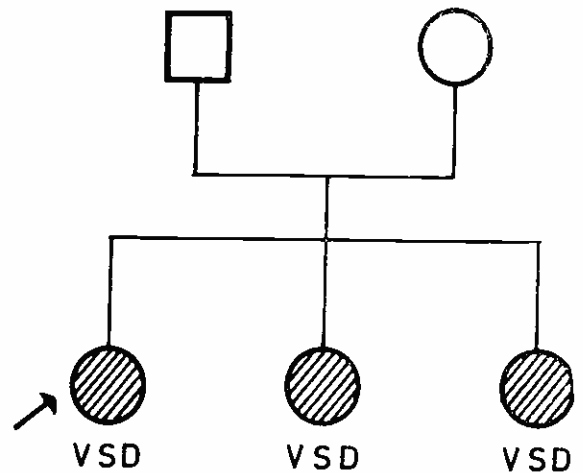


Fig. 4. Family with all 3 offspring with V.S.D.

of the risk in the commonest anomaly, the rest being less than this, so that the risk may be worth taking in most instances. However, when the next offspring is affected, the risk now rises because a greater risk family with a multifactorially inherited disease now reveals itself. For example, Family P (Fig. 3) had a first child (a son) who was found to be suffering from PDA with P.S., which gives an empirical risk of 1 in 30 for the next child to be affected for PDA. The risk was taken and the next child was a girl, and unfortunately she also was found to be suffering from PDA. What then is the risk for the next baby to be affected? The risk rises and in this situation, it now becomes 1 in 7, i.e. the risk is trebled when there are 2 siblings affected. Or again, there is another family (Family Q) (Fig. 4) where 3 children, all girls, were born with VSD. The risk for the next offspring to be affected now is 10 times as great, i.e. it is 1 in 2. It will be noticed that the risk now approximates that due to inheritance of genes of large mutant effect—autosomal dominant.

CONCLUSION:

In the last decade aetiological factors in CHD have been clarified to such an extent that primary prevention is now possible. Admittedly not all causes are fully known, but with greater emphasis in research in this area, it is to be hoped that this crippling disease entity will be largely prevented in the future.

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